Results of surgical treatment for recurrent differentiated thyroid cancer at National Hospital of Endocrinology

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Abstract

Introduction: To evaluate the results of surgical treatment for recurrent differentiated thyroid cancer.

Patients and methods: Descriptive study of 82 recurrent differentiated thyroid cancer patients underwent re-operated at National Hospital of Endocrinology from 2017 to 2020.

Results: Mean age 44.2 ± 12.6 years, female/male = 3.3/1. Median recurrence times was 25 months. Patients detected the disease through regular health check was 82.9%. Physical examination revealed lesions 31,7%. Ultrasound revealed lesions 97.6%. Tg positive 81.7%, median 33.2; Anti-Tg positive 20.7%, median 22.6. Whole-body Scintigraphy was positive 47.6%. PET/CT positive 100%. Surgical techniques: Total thyroidectomy + cervical lymph nodes dissection accounted for 9.8%; cervical lymph nodes dissection only accounted for 90.2%. Location of cervical lymph node dissection: Central dissection 18.3%; lateral dissection 51.2%; Central & lateral lymph nodes dissection accounted for 30.5%. The rate of invasion of recurrent block accounted for 23.2%. Complications that occurred during surgery including: major vascular injury 2.4%; laryngeal nerve injury 2.4%, tracheal injury 1.2%, parathyroid glands injury 3.6%, lymphatic vascular injury 6.1% were managed immediately during surgery. Post-surgical complications: bleeding 1.2%; respiratory failure 1.2%; hoarseness 3.6%; Hypocalcemia 11.0%; Hematoma 3.6%; Chyle leak 7.3%, in which 1 case (1.2%) had to have stitches sutured. Vocal fold paralysis after in 3 months later (2.4%) and 1 case hypoparathyroidism (1.2%); Tg positive 70.7%, median 14.3. Anti–Tg positive 13.4%, median 16.2. 18.3% of patients treated with hormone only; 81.7% of patients treated with I^{131}.

Conclusion: Surgery is a safe and effective treatment for recurrent differentiated thyroid cancer.

Keywords: Recurrent differentiated thyroid cancer, lymph node neck dissection

Introduction

Thyroid cancer is the most common malignancy of the endocrine system, with an increasing trend globally, accounting for about 90% of all endocrine cancers and 3.6% of all cancers [1,2]. Although differentiated thyroid cancer has a good prognosis due to its slow progression, curable resection, and response to I^{131} therapy, recent studies have shown that about 10 to 30% of patients have recurrences. Recurrent differentiated thyroid cancer is the presence of one or more lesions in the thyroid gland, cervical lymph node system or other sites in a patient who has been previously diagnosed with thyroid cancer and treated as completely removed cancer tissue (thyroid tissue can be removed with or without cervical lymphadenectomy, with or without I^{131}) with time from the first treatment to the time of recurrence more than 6 months [3, 4]. The cause of the high recurrence may be due to increasing resistance to I^{131} and it is related to the outcome of first-time surgery. Neck ultrasound, quantification of Tg, Anti-Tg and whole body scintigraphy are first-line tests to diagnose recurrent differentiated thyroid cancer. The issue of treatment of recurrent differentiated thyroid cancer is still debated about when to treat? Which treatment method should be used to balance the benefits of treatment with the risks of complications? This issue is still a challenge for clinicians and requires the participation of many specialties. In general, the mainstay of treatment in recurrent differentiated carcinoma is I^{131} and surgery in which surgery is the important method to remove the lesion [3-5]. Surgery for recurrent thyroid cancer is often difficult due to anatomical changes, fibrosis after previous surgery and invasion of cancer, so the rate of complications is often high. Good preparation before surgery with diagnostic image tests to locate lesions, experienced and skilled surgeons can control the recurrent lesions, reduce the complications, and improve the efficiency of treatment.

Research subjects and methods

Research subjects

There were 82 patients with differentiated thyroid cancer who have been previously treated with thyroid tissue resection, with or without cervical lymphadenectomy, with or without I^{131} therapy enrolled. The patients were diagnosed with neck recurrence and had surgery to remove the recurrent lesion at the National Hospital of Endocrinology from January 2017 to the end of December 2020.

Criteria for selection

Patients with a diagnosis of differentiated thyroid cancer who have undergone total thyroidectomy, with or without cervical lymphadenectomy, with or without I^{131} therapy, with completed records or documents proving the previous treatment.

Diagnosis of recurrence is demonstrated by diagnostic imaging and pathology.

The patient underwent surgery to remove the recurrent lesions.

Full medical records.

There is follow-up information after treatment.

Research Methods

Study design: descriptive study.

Study sample size: convenient sample size.

Data collection: All patients eligible for the study were collected information according to a uniform medical record including clinical, subclinical, surgical methods, postoperative complications and final results..

Data processing: The data was processed using the software SPSS 20.0.

Results and discussion

Clinical and paraclinical features

Clinical features

Age and gender: The mean age in our study was 44.2 ± 12.6 years old (19 - 77), patient group < 45 years old 56.1%. This result is consistent with the study of Doan Van Lam, 40 ± 12 years old (15 - 64 years old), 60,7% group of patients < 45 years old [5]. The mean age in Hughes and Lang's study was 37.6 (16 – 75) and 54.2 (18 – 85) [3, 6]. The female/

male ratio in our study was 3.3/1 compared with that in Hughes' study was 2.2/1 [3]; Lang 2.3/1 and Doan Van Lam 2.7/1 [5].

Reason for hospitalization: The majority of patients were detected the disease through routine health check 82.9%. The most common functional sign was dysphgia 17.5%.

Time to relapse: Median time to relapse was 25 months, relapse in the first 2 years was 52.5%; the earliest was 6 months, the latest was 216 months. Through these results, relapse can occur at any time, so periodic examination for the rest of life is essential. This result is consistent with Su-jin Kim's study, the average relapse time is 25.3 months [7], according to Le Van Quang, relapse usually occurs in the first 2 years (lead [4]).

Characteristics of pre-treatment: 100% total excision of thyroid; cervical lymphadenectomy was 69.5%, lymph node dissection was mainly in the central and lateral compartments on one side, 59.6%. According to Doan Van Lam, total thyroidectomy was in 100%; cervical lymphadenectomy 73.1%; location of lymph node dissection on one side 46.1% [5]. According to Duong Chi Thanh, cervical lymph node dissection was 55.5%; The main location of the central compartment & the one-sided lateral compartment is 86.7% [4]. Histopathology papillary 97.6%. There were two patients (2.4%) with vocal cord paralysis, no patient had permanent hypoparathyroidism. Stage T3 accounts for a high rate of 43.9%; N1 lymph nodes 64.6%. 75.6% had I^{131} therapy, median dose 150 mCi.

Clinical characteristics of recurrent mass: Clinical examination revealed lesions 31.7%; solid density 96.2%, limited mobility 69.2%; boundary unknown 61.5%. Research results of Duong Chi Thanh: clinical examination found 33.3%; solid density 76.2%; limited mobility 71.5%; unknown boundary 57.1% [4].

Subclinical features:

According to the treatment process of patients with differentiated thyroid cancer, after surgical removal of whole thyroid gland ± I^{131} treatment, the patient will be monitored clinically, tested for Tg, Anti-Tg and diagnostic imaging check (neck ultrasound, X-ray). If the patient responds completely, periodic follow-up will be continued. If the patient has clinically and/or ultrasound suspicious lymph nodes, fine needle aspiration cytology will be indicated for diagnosis. CT scan is usually indicated when there is a suspicion of recurrent mass invading the neck or lung metastases. If the patient is negative on both clinical, ultrasound and X-ray while Tg levels are still elevated, PET/CT will be indicated.

Ultrasound of the neck areas: Ultrasound is very valuable in identifying recurrent thyroid cancer, it can detect recurrent masses as small as < 1 cm or deep in locations that are not detectable by physical examination with images such as hilar lymph node structure unknown, microcalcification, irregular margin, invasion... In our series, the detection rate of recurrent lesions on ultrasound was 97.6%. This result is similar to the study of Hughes 94.4% [3]; Doan Van Lam 96.6% [5] (Table 1). Ultrasound detected mass at the thyroid bed in 8 cases (9.8%); average size 18.3 ± 10.2mm. Ultrasound detected abnormal cervical lymph nodes in 79 cases (96.3%); The average lymph node size was 15.4 ± 6.3mm, most of the lymph nodes recurred in the lateral compartment in 73.4%.

Levels of Tg and Anti-Tg: Serum Tg is the most sensitive biomarker in the diagnosis of recurrent differentiated carcinoma of the thyroid cancer after total thyroidectomy ± I^{131} therapy, rapidly increasing Tg is specific for disease progression. In our study, stimulated Tg ≥ 10 ng/mL accounted for 81.7%; median 33.2 ng/mL is greater than Hughes's 20.7 ng/ml [3]; 43 ng/ml lower than Doan Van Lam (anti-Tg group) [5]. In addition to the Tg value, it is necessary to quantify Anti-Tg because when Anti-Tg increases, there will be a corresponding amount of Tg combined with Anti-Tg to reduce the concentration of Tg artificially, so it will falsify the results of Tg quantification. The rate of positive Anti-Tg in this study was 20.7%; median 22.6 IU/mL is similar to the study of Doan Van Lam 23.4% [5]; Lang 20.1% [6].

Table 1. Recurrent features among the different reports

	Hughes (2012)	D.V. Lam (2016)	Duong Chi Thanh (2017)	In this study
Neck ultrasound	54	145	54	82
Normal	3 (5,6%)	5 (3,4%)	5 (9,3%)	2 (2,4%)
Positive	51 (94,4%)	140 (96,6%)	49 (90,7%)	80 (97,6%)
Full body scintigraphy	51	139	41	82
Negative	26 (50,9%)	110 (75,9%)	18 (43,9%)	43 (52,4%)
Positive	25 (49,1%)	29 (24,1%)	23 (56,1%)	39 (47,6%)
Neck CT scan	36			76
Negative	3 (8,3%)	*	*	4 (5,3%)
Positive	33 (91,7%)	*	*	72 (94,7%)
PET/CT	36	11	18	2
Negative	3 (8,3%)	0 (0,0%)	0 (0,0%)	0 (0,0%)
Positive	33 (91,7%)	11 (100%)	18 (100%)	2 (100%)

Full body scintigraphy: is one of the necessary tests to evaluate the bilan for patients with recurrent differentiated thyroid cancer, it can detect local, regional and distant metastatic recurrence. However, according to the authors, the ability to detect cervical lymph node recurrence by scintigraphy is relatively low. In our study, all the patients were done full body scintigraphy with positive results 47.6%. This result is consistent with the study of Duong Chi Thanh 56.1% [4]; Hughes 49.1% [3] (Table 1).

PET/CT: indicated in the case of ultrasound, rectal X-ray does not detect lesions but serum Tg, Anti-Tg levels are still high. In our study, PET/CT was performed in 2 patients with positive cervical lymph node results (Table 1).

Neck CT scan : 76/82 patients had a CT scan of the neck, the lesion detection rate was 94.7% (Table 1). The recurrence detection rate of CT is lower than that of ultrasound but is more valuable in invasive detection.

Cytogram: In our study, cytology at the cervical lymph node gave a positive result of 90.2%. This result is equivalent to the positive study of Duong Chi Thanh 89.2% [4]. According to Hughes' study, 32 patients (52.5%) underwent ultrasound-guided cytology with 100% positive results [3].

Treatment results

Surgical method

The selected surgical method must minimize the risk of recurrence, facilitate the treatment of I^{131} and the post-operative follow-up. In our study, cervical lymph node dissection alone accounted for a high rate of 90.2% because the disease mainly recurred in the lymph nodes (Figure 1). This rate according to Duong Chi Thanh's research is 66.7% [4]; Lang's is 88% [6].

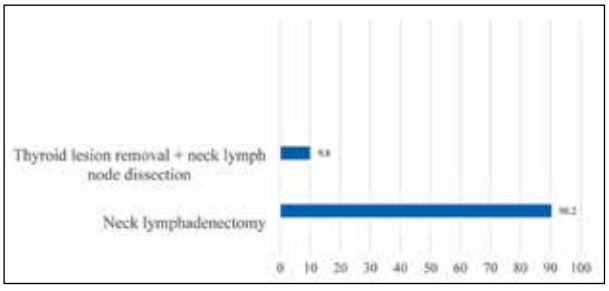

Chart 1. Surgical method

Location of cervical lymphadenectomy: according to the American Thyroid Association's recommendation, in recurrent thyroid cancer, if lymphadenectomy is indicated, lymph node dissection should be performed in each anatomical compartment if possible. Dissection of the cervical lymph nodes in both mediastinum and lateral spaces minimizes the risk of lymph node survival and recurrence [2]. In our study, there were 15 patients with cervical lymphadenectomy (18.3%); 42 patients with lateral cervical lymphadenectomy (51.2%) and 25 patients with cervical lymphadenectomy both mediastinum and lateral compartment (30.5%).

This result is similar to the study of the author Hughes to harvest the cervical lymph nodes in the mediastinum compartment 18%; side compartment 49.2%; both mediastinum and lateral compartments 32.8% (Table 2).

Table 2. Lymph node dissection locations among authors

Lymph node dissection site	Hughes (2012) [3]	Lang (2013) [6]	Doan Van Lam (2016) [5]	Our study
Mediastinum	11 (18%)	20 (45,5%)	63 (43,4%)	15 (18,3%)
Lateral compartment	30 (49,2%)	0	63 (43,4%)	42 (51,2%)
Mediastinum and lateral compartment	20 (32,8%)	24 (54,5%)	19 (13,1%)	25 (30,5%)

Location of recurrence

Compared with the results of recurrent sites after surgery, in our study, the recurrence location at the thyroid bed was only 3.7%; recurrence in the cervical lymph nodes alone 90.2% ; Recurrence at both thyroid bed and cervical lymph nodes was 6.1%. This result is different from Duong Chi Thanhs report, this rate was 14.8%, respectively; 66.7% and 18.5% [4]. The recurrence rate in Duong Chi Thanh's tumor is higher than ours, which is explained by the fact that in the study sample, the author took a patient with a thyroidectomy, moreover, because the technique and experience of the surgeon for removal of thyroid tissue is getting better and better also reduce local recurrence. According to Lin JD, each recurrence site is associated with different prognostic factors, risk factor studies have shown that papillary carcinoma is more likely to recur in regional lymph nodes, and follicular cancer is more likely to metastasize than papillomatosis, recurrence is associated with first-line surgery, and the experience of the surgeon markably influences (referred to [4]).

Table 3. Invasive characteristics

	Invasion at thyroid bed		Invasion of lymph nodes	
	Number of patients	Ratio (%)	Number of patients	Ratio (%)
Noninvasive	4	50,0	67	81,7
Muscles,soft tissues	3	37,5	9	11,0
Nerve	1	12,5	2	2,4
Vascular	0	0,0	4	4,9
Trachea	0	0,0	0	0,0

In our study, there were 4/8 patients (50%) recurrence at thyroid bed with invasion, of which 3 patients (37.5%) had invasion in muscle and one patient (12.5%) had invasion in nervous system (Table 2). The rate of lymph node invasion was 18.3%, including 9 patients with muscle invasion (11%), 2 patients with nerve invasion (2.4%), 4 patients with vascular invasion (4.9%) (Table 3). The results of Duong Chi Thanh's study showed the invasion rate of tumors and lymph nodes was 22.3% and 11.3% [4]. The study results reported that the invasion rate of tumor and lymph node was relatively high in the cases of recurrence. The invasive condition makes surgery difficult, increasing the rate of accidents and complications.

Incidents and complications

Table 4. Incidents

Incidents	Number of patients	Rate (%)
Injury to major vessels	2	2,4
Traumatic nerve cord injury	2	2,4
Parathyroid gland damage	3	3,6
Tracheal injury	1	1,2
Lymphatic injury	5	6,1

Incidents: There were 2 patients (2.4%) with major vascular lesions; two patients (2.4%) had traumatic nerve cord injury, 3 (3.6%) parathyroid gland damage, one (1.2%) tracheal injury and 5 (6.1%) patients with lymphatic injury (Table 4). All incidents were all treated during surgery: hemostasis, repair of nerve cord, re-implantation of the parathyroid gland, suture of the trachea and lymphatic vessels. Hughes' study had one patient (1.6%) died in surgery, one patient (1.6%) had traumatic nerve cord injury, and 4 patients (6.5%) had parathyroid gland damage.

Table 5. Complications

Complications	First weeks		One month		Three months	
	n	%	n	%	n	%
Bleeding	1	1,2	0	0,0	0	0,0
Hoarseness	3	3,6	3	3,6	2	2,4
Numbness in limbs	9	11,0	1	1,2	1	1,2
Respiratory failure	1	1,2	0	0,0	0	0,0
Chyle leak	6	7,3	0	0,0	0	0,0
Hematoma	3	3,6	0	0,0	0	0,0

Complications: The rate of complications was highest in the first week and then gradually decreased (Table 5). There was one patient (1.2%) bleeding in the first day after surgery, the patient was treated with emergency surgery to stop the bleeding. One patient with respiratory failure (1.2%) had to re-intubate, after 3 days of withdrawal, the patient was stable. In this case, during surgery, we clearly identified the recurrent nerve cord, so we decided not to open the trachea immediately, the patient had difficulty breathing, possibly because the trachea was soft and collapsed. There were 6 patients (7.3%) chylous leak, of which 6 patients had small fistula, medical treatment; one patient (1.2%) required surgery to suture the fistula. There were 3 patients (3.6%) collecting wound fluid (hematoma), 3 patients (3.6%) were very hoarse, these patients were treated with anti-edema, Solumedrol. Re-examination after 3 months left 2 patients (2.4%) hoarse voice, otolaryngoscopy reduced vocal cord movement on one side. The rate of limb numbness in the first day was 3.6%; this rate increased in the following days, the highest was 11%; Patients were injected with intravenous calcium in the first days combined with Calcitriol, symptoms gradually decreased. Re-examination after 3 months, there was 1 patient (1.6%) of numbness in the limbs, blood calcium ion concentration and PTH (Parathyroid Hormone) decreased. Our rate of limb numbness is similar to that of Lang, Tufano and Doan Van Lam, this rate is 14%, 12.5% and 11.7%, respectively [5, 6, 8]. (Table 6)

The results show that the complication rate in our study is within the allowable limit and is similar to that of the authors (Table 6). Surgery for recurrent differentiated thyroid cancer was indicated according to ATA (American Thyroid Association) guidelines with acceptable safety because most complications are temporary. However, before surgery, it is necessary to carefully advise the patient about the permanent complications that may occur long-term affecting the quality of life such as vocal cord paralysis, permanent hypoparathyroidism, especially in cases of recurrent invasive mass.

Evaluation after surgery

After surgery, all patients were scheduled to be re-examined to check the incision, other complications, neck ultrasound, Tg, Anti-Tg to evaluate the effectiveness of surgical treatment. There were 15 cases (18.3%) clinical, negative diagnostic imaging and stimulation Tg < 10 ng/mL, Anti-Tg negative: the patients received hormone therapy and scheduled for periodic follow-up; 67 cases (81.7%) continued to receive I^{131} treatment.

Table 6. Complications of re-surgery among authors

Complications	Roh [9]	Shah [10]	Tufano [8]	Doan Van Lam [5]	Duong Chi Thanh [4]	Our study
Bleeding	*	*	*	*	1,9	1 (1,2)
Respiratory failure	*	*	*	*	1,9	1 (1,2)
Hoarseness						
Temporary	22,2	3,7	5,8	6,9	10,8	3 (3,6)
After 3 months	17,8	3,7	5,8	1,4	0,0	2 (2,4)
Lower Calci						
Temporary	46,3	20,7	10,0	11,0	9,0	9 (11,0)
After 3 months	4,9	7,3	2,5	0,7	0,0	1 (1,2)
Chyle leak	*	*	*	0,7	1,9	6 (7,3)
Hematoma	*	*	*	*	*	3 (3,6)

Conclusion

Surgery is a safe and effective treatment method in the management of recurrent differentiated thyroid cancer.

Conflict of interest: The authors declare that they have no conflict of interest.

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